

BMS PH-7048 A (C) RESPONSE TO RESTRICTION (Feb 8, 2005) AND AMENDMENT

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1. (CURRENTLY AMENDED) A method of screening for inhibitors of beta-amyloid production comprising,

- 1) contacting a potential inhibitor of beta-amyloid production and a tagged inhibitor of beta-amyloid production with at least one macromolecule involved in the processing of APP and the production of beta-amyloid peptide, wherein the macromolecule is a secretase selected from alpha-secretase, beta secretase, and gamma-secretase, said macromolecule containing a binding site specific for said tagged inhibitor of beta-amyloid production;
- 2) separating the tagged inhibitor of beta-amyloid production bound to said macromolecule from the tagged inhibitor of beta-amyloid production free from said macromolecule; and
- 3) determining an inhibitory concentration of the potential inhibitor of beta-amyloid production from the concentration of tagged inhibitor of beta-amyloid production bound to said macromolecule.

2. (ORIGINAL) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a radiolabeled inhibitor of beta-amyloid production, a fluorescence labeled inhibitor of beta-amyloid production or a biotin labeled inhibitor of beta-amyloid production.

3. (ORIGINAL) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a radiolabeled inhibitor of beta-amyloid production.

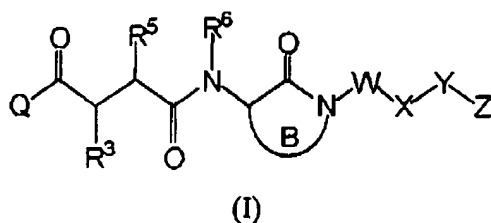
4. (ORIGINAL) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a tritium or iodine radiolabeled inhibitor of beta-amyloid production.

5. (ORIGINAL) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a tritium radiolabeled inhibitor of beta-amyloid production.

6. (CURRENTLY AMENDED) The method of Claim 1 wherein the tagged inhibitor of beta-amyloid production comprises a compound of the Formula (I):

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wherein:

at least one atom of the compound of the Formula (I) is radiolabeled;

Q is NH₂;

R³ is C₁-C₆ alkyl substituted with 0-1 R⁴;

R⁴ is H, OH, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₁₀ carbocycle, C₆-C₁₀ aryl, or 5 to 10 membered heterocycle;

R⁵ is H, OR¹⁴;

C₁-C₆ alkyl substituted with 0-3 R^{5b};

C₁-C₆ alkoxy substituted with 0-3 R^{5b};

C₂-C₆ alkenyl substituted with 0-3 R^{5b};

C₂-C₆ alkynyl substituted with 0-3 R^{5b};

C₃-C₁₀ carbocycle substituted with 0-3 R^{5c};

C₆-C₁₀ aryl substituted with 0-3 R^{5c}; or

5 to 10 membered heterocycle substituted with 0-3 R^{5c};

R^{5b}, at each occurrence, is independently selected from:

H, C₁-C₆ alkyl, CF₃, OR¹⁴, Cl, F, Br, I, =O, CN, NO₂, NR¹⁵R¹⁶;

C₃-C₁₀ carbocycle substituted with 0-3 R^{5c};

C₆-C₁₀-aryl substituted with 0-3 R^{5c}; or

5 to 10 membered heterocycle substituted with 0-3 R^{5c};

R^{5c}, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F,

Br, I, CN, NO₂, NR¹⁵R¹⁶, or CF₃;

R⁶ is H;

C₁-C₆ alkyl substituted with 0-3 R^{6a};

C₃-C₁₀ carbocycle substituted with 0-3 R^{6b}; or

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~~C₆-C₁₀~~ aryl substituted with 0-3 R^{6b};

R^{6a}, at each occurrence, is independently selected from H, C₁-C₆ alkyl, OR¹⁴, Cl, F, Br, I, =O,

CN, NO₂, NR¹⁵R¹⁶, phenyl or CF₃;

R^{6b}, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F,

Br, I, CN, NO₂, NR¹⁵R¹⁶, or CF₃;

W is -(CR⁸R^{8a})_p-;

p is 0 to 4;

R⁸ and R^{8a}, at each occurrence, are independently selected from H, C₁-C₄ alkyl, C₂-C₄ alkenyl,

C₂-C₄ alkynyl and C₃-C₈ cycloalkyl;

X is a bond;

C₆-C₁₀ aryl substituted with 0-3 R^{Xb};

C₃-C₁₀ carbocycle substituted with 0-3 R^{Xb}; or

5 to 10 membered heterocycle substituted with 0-3 R^{Xb};

R^{Xb}, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl,

F, Br, I, CN, NO₂, NR¹⁵R¹⁶, or CF₃;

Y is a bond or -(CR⁹R^{9a})_t-V-(CR⁹R^{9a})_u-;

t is 0 to 3;

u is 0 to 3;

R⁹ and R^{9a}, at each occurrence, are independently selected from H, C₁-C₆ alkyl or C₃-C₈

cycloalkyl;

V is a bond, -C(=O)-, -O-, -S-, -S(=O)-, -S(=O)₂-, -N(R¹⁹)-, -C(=O)NR^{19b}-, -NR^{19b}C(=O)-, -

NR^{19b}S(=O)₂-, -S(=O)₂NR^{19b}-, -NR^{19b}S(=O)-, -S(=O)NR^{19b}-, -C(=O)O-, or -OC(=O)-;

Z is H;

C₁-C₈ alkyl substituted with 0-2 R¹²;

C₂-C₄ alkenyl substituted with 0-2 R¹²;

C₂-C₄ alkynyl substituted with 0-2 R¹²;

~~C₆-C₁₀~~ aryl substituted with 0-4 R^{12b};

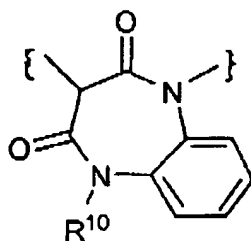
C₃-C₁₀ carbocycle substituted with 0-4 R^{12b}; or

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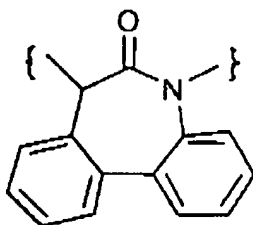
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5 to 10 membered heterocycle substituted with 0-3 R^{12b} ; R^{12} is C_6 - C_{10} aryl substituted with 0-4 R^{12b} ; C_3 - C_{10} carbocycle substituted with 0-4 R^{12b} ; or5 to 10 membered heterocycle substituted with 0-3 R^{12b} ; R^{12b} , at each occurrence, is independently selected from H, OH, C_1 - C_6 alkyl, C_1 - C_4 alkoxy, Cl,F, Br, I, CN, NO_2 , $NR^{15}R^{16}$, or CF_3 ;

B is



or



~~a 5 to 10 membered lactam, wherein the lactam is saturated, partially saturated or unsaturated;~~
~~wherein each additional lactam carbon is substituted with 0-2 R^{11} ; and, optionally, the~~
~~lactam contains a heteroatom selected from O, S, $S(=O)$, $S(=O)_2$, N, and~~
 ~~$N(R^{10})$;~~

 R^{10} is H, $C(=O)R^{17}$, $C(=O)OR^{17}$, $C(=O)NR^{18}R^{19}$, $S(=O)_2NR^{18}R^{19}$, $S(=O)_2R^{17}$; C_1 - C_6 alkyl optionally substituted with R^{10a} ; C_6 - C_{10} aryl substituted with 0-4 R^{10b} ; C_3 - C_{10} carbocycle substituted with 0-3 R^{10b} ; or

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5 to 10 membered heterocycle optionally substituted with 0-3 R^{10b};

R^{10a}, at each occurrence, is independently selected from H, C₁-C₆ alkyl, C₃-C₆ cycloalkyl, OR¹⁴, Cl, F, Br, I, =O, CN, NO₂, NR¹⁵R¹⁶, phenyl or CF₃;

R^{10b}, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F, Br, I, CN, NO₂, NR¹⁵R¹⁶, or CF₃;

~~R¹¹ is C₁-C₄ alkoxy, Cl, F, Br, I, =O, CN, NO₂, NR¹⁸R¹⁹, C(=O)R¹⁷, C(=O)OR¹⁷, C(=O)NR¹⁸R¹⁹, S(=O)₂NR¹⁸R¹⁹, CF₃;~~

~~C₁-C₆ alkyl optionally substituted with R^{11a};~~

~~C₆-C₁₀ aryl substituted with 0-3 R^{11b};~~

~~C₃-C₁₀ carbocycle substituted with 0-3 R^{11b}; or~~

~~5 to 10 membered heterocycle substituted with 0-3 R^{11b};~~

~~alternatively, two R¹¹ substituents on the same carbon atoms may be combined to form a C₃-C₆ carbocycle;~~

~~alternatively, two R¹¹ substituents on adjacent carbon atoms may be combined to form a C₃-C₆ carbocycle or a benzo fused radical, wherein said benzo fused radical is substituted with 0-3 R¹³;~~

~~R^{11a}, at each occurrence, is independently selected from H, C₁-C₆ alkyl, OR¹⁴, Cl, F, Br, I, =O, CN, NO₂, NR¹⁵R¹⁶, phenyl or CF₃;~~

~~R^{11b}, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F, Br, I, CN, NO₂, NR¹⁵R¹⁶, or CF₃;~~

~~R¹³, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, C₁-C₄ alkoxy, Cl, F, Br, I, CN, NO₂, NR¹⁵R¹⁶, or CF₃;~~

R¹⁴ is H, phenyl, benzyl, C₁-C₆ alkyl, or C₂-C₆ alkoxyalkyl;

R¹⁵, at each occurrence, is independently selected from H, C₁-C₆ alkyl, benzyl, phenethyl, -C(=O)-(C₁-C₆ alkyl) and -S(=O)₂-(C₁-C₆ alkyl);

R¹⁶, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, benzyl, phenethyl, -C(=O)-(C₁-C₆ alkyl) and -S(=O)₂-(C₁-C₆ alkyl);

R¹⁷ is H, phenyl, benzyl, C₁-C₆ alkyl, or C₂-C₆ alkoxyalkyl;

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R¹⁸, at each occurrence, is independently selected from H, C₁-C₆ alkyl, benzyl, phenethyl, -C(=O)-(C₁-C₆ alkyl) and -S(=O)₂-(C₁-C₆ alkyl); and

R¹⁹, at each occurrence, is independently selected from H, OH, C₁-C₆ alkyl, phenyl, benzyl, phenethyl, -C(=O)-(C₁-C₆ alkyl) and -S(=O)₂-(C₁-C₆ alkyl);

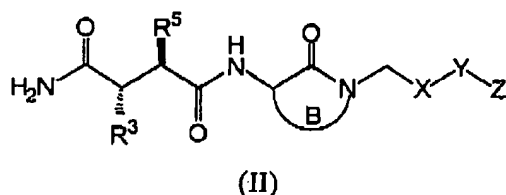
R^{19b} is H, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, phenyl, benzyl or phenethyl; and

R²⁰ is H or C₁-C₆ alkyl.

7. (ORIGINAL) The method of Claim 6 wherein R³ is C₃-C₆ alkyl.

8. (ORIGINAL) The method of Claim 6 wherein R³ is C₃-C₆ alkyl substituted with about 1 to about 4 ³H.

9. (ORIGINAL) The method of Claim 6 wherein the tagged inhibitor of beta-amyloid production comprises a compound of the Formula (II):



wherein:

at least one atom of the compound of the Formula (II) is radiolabeled.

10. (ORIGINAL) The method of Claim 9 wherein R³ is C₃-C₆ alkyl substituted with about 1 to about 4 ³H.

11. - 12 (CANCELLED)

13. (CURRENTLY AMENDED) The method of Claim 1 wherein at least one macromolecule involved in the processing of APP and the production of beta-amyloid peptide comprises alpha, beta or gamma-secretase ~~presenilin 1 or a fragment of presenilin 1.~~

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14. (CURRENTLY AMENDED) The method of Claim 1 wherein at least one macromolecule involved in the processing of APP and/or the production of beta-amyloid peptide ~~comprises~~ comprises:

- (1) ~~presenilin-1;~~
- (2) ~~presenilin-2;~~
- (1) (3) β secretase;
- (2) (4) α secretase; or
- (3) (5) γ secretase; ~~or~~
- (6) ~~BACE/memapsin-2;~~

or any fragment or derivative thereof.

15. (ORIGINAL) The method of Claim 1 wherein the inhibitory concentration is half maximal inhibitory concentration.

16. (ORIGINAL) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of an inhibitor of beta-amyloid production identified by the screening assay of Claim 1 or a pharmaceutically acceptable salt or prodrug form thereof.

17. (CURRENTLY AMENDED) A method for treating degenerative neurological disorders involving beta-amyloid production comprising administering to a host in need of such treatment a therapeutically effective amount of an inhibitor of beta-amyloid production identified by the screening assay of Claim 1 or a pharmaceutically acceptable salt ~~or prodrug~~ form thereof.

18. (CURRENTLY AMENDED) A method for treating Alzheimer's disease comprising administering to a host in need of such treatment a therapeutically effective amount of an inhibitor of beta-amyloid production identified by the screening assay of Claim 1 or a pharmaceutically acceptable salt ~~or prodrug~~ form thereof.

19. (CANCELLED)

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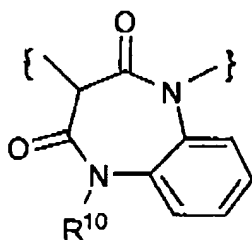
20. (CURRENTLY AMENDED) The method of Claim ~~1~~ 1 wherein the tagged inhibitor of beta-amyloid production comprises a radiolabeled inhibitor of beta-amyloid production, a fluorescence labeled inhibitor of beta-amyloid production, or a biotin labeled inhibitor of beta-amyloid production, ~~a photoaffinity labeled inhibitor of beta-amyloid production, or any combination of tags thereof in one inhibitor of beta-amyloid production.~~

21. (CURRENTLY AMENDED) The method of Claim ~~1~~ 1 wherein the tagged inhibitor of beta-amyloid production comprises a radiolabeled inhibitor of beta-amyloid production.

22. (CURRENTLY AMENDED) The method of Claim ~~1~~ 1 wherein the tagged inhibitor is radiolabeled with one or more radioisotope selected from ^3H , ^{11}C , ^{14}C , ^{18}F , ^{32}P , ^{35}S , ^{123}I , ^{125}I , or ^{131}I of beta-amyloid production ~~comprises a tritium labeled inhibitor of beta-amyloid production.~~

23.-35. (CANCELLED)

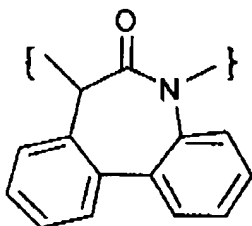
36. (CURRENTLY AMENDED) An inhibitor of beta-amyloid production comprising a compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula (I) ~~(I-7T) or (I-43T) wherein m is about 2 as claimed in claim 1 wherein ring B is~~



or

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37. (CURRENTLY AMENDED) An inhibitor of beta-amyloid production of Claim 36 wherein the macromolecule involved in the production of beta-amyloid peptide is alpha-secretase, beta-secretase, or gamma-secretase, presenilin-1 or a fragment thereof presenilin-1.

38. (CURRENTLY AMENDED) An inhibitor of beta-amyloid production of Claim 36 wherein the macromolecule involved in the production of beta-amyloid peptide is gamma-secretase presenilin-2 or a fragment thereof presenilin-2.

39. (CURRENTLY AMENDED) An inhibitor of beta-amyloid production of Claim 36 comprising a compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula (I-7T) wherein m is about 2; and the compound demonstrates a half maximal inhibitory concentration less than 10 micromolar for beta-amyloid production.

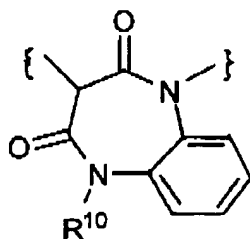
40. (CURRENTLY AMENDED) An inhibitor of beta-amyloid production of Claim 36 comprising a compound which interacts with a binding site on gamma-secretase presenilin-1 or a fragment of gamma-secretase presenilin-1; wherein said binding site is a specific binding site for a compound of Formula (I-7T) wherein m is about 2; and the compound demonstrates a half maximal inhibitory concentration less than 10 micromolar for beta-amyloid production.

41. (CURRENTLY AMENDED) An inhibitor of beta-amyloid production of Claim 36 6 comprising a compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula (I-43T) wherein B is m is about 2

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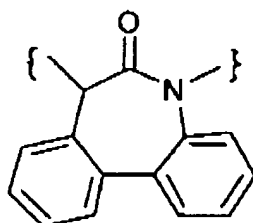
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and the compound demonstrates a half maximal inhibitory concentration less than 10 micromolar for beta-amyloid production.

42. (CURRENTLY AMENDED) An inhibitor of beta-amyloid production of Claim 36 6 comprising a compound which interacts with a binding site on ~~gamma-secretase presenilin-1~~ or a fragment of ~~gamma-secretase presenilin-1~~; wherein said binding site is a specific binding site for a compound of Formula (I-43T) wherein ~~m is about 2~~ B is

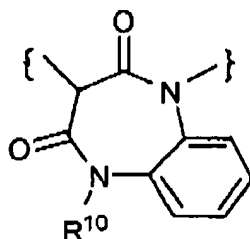


and the compound demonstrates a half maximal inhibitory concentration less than 10 micromolar for beta-amyloid production.

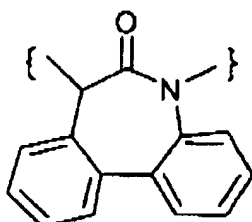
43. (CURRENTLY AMENDED) A tagged inhibitor of beta-amyloid production of Claim 6 comprising a tagged compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula (I) ~~(I-7T) or (I-43T)~~ wherein ~~m is about 2~~ ring-B is:

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or



44. (CURRENTLY AMENDED) A tagged inhibitor of beta-amyloid production of Claim 43 wherein the macromolecule involved in the production of beta-amyloid peptide is alpha-, beta-, or gamma-secretase presenilin-1 or a fragment thereof presenilin-1.

45. (CURRENTLY AMENDED) A tagged inhibitor of beta-amyloid production of Claim 43 wherein the macromolecule involved in the production of beta-amyloid peptide is gamma-secretase presenilin-2 or a fragment thereof presenilin-2.

46. (CURRENTLY AMENDED) A tagged inhibitor of beta-amyloid production of Claim 43 comprising a tagged compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said ~~binding site is a specific binding site for a compound of Formula (I-7T) wherein m is about 2; and the tagged compound demonstrates a~~ half maximal inhibitory concentration less than 10 micromolar for beta-amyloid production.

47. (CURRENTLY AMENDED) A tagged inhibitor of beta-amyloid production of Claim 43 comprising a tagged compound which interacts with a binding site on alpha-, beta-, or gamma-

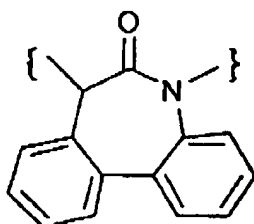
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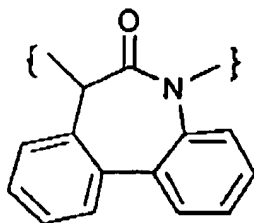
secretase presenilin-1 or a fragment thereof presenilin-1; wherein said binding site is a specific binding site for a compound of Formula (I-7T) wherein m is about 2; and the tagged compound demonstrates a half maximal inhibitory concentration less than 10 micromolar for beta-amyloid production.

48. (CURRENTLY AMENDED) A tagged inhibitor of beta-amyloid production of Claim 6 ~~43~~ comprising a tagged compound which interacts with a binding site on a macromolecule involved in the production of beta-amyloid peptide; wherein said binding site is a specific binding site for a compound of Formula (I) (~~I-43T~~) wherein m is about 2 ring B is



and the tagged compound demonstrates a half maximal inhibitory concentration less than 10 micromolar for beta-amyloid production.

49. (CURRENTLY AMENDED) A tagged inhibitor of beta-amyloid production of Claim 48 ~~43~~ comprising a tagged compound which interacts with a binding site on presenilin 1 or a fragment of presenilin 1; wherein said binding site is a specific binding site for a compound of Formula (I) (~~I-43T~~) wherein m is about 2 ring B is:



and the tagged compound demonstrates a half maximal inhibitory concentration less than 10 micromolar for beta-amyloid production.

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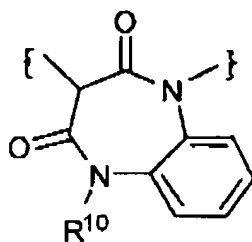
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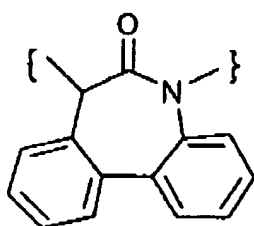
50. – 53. (CANCELLED)

54. (CURRENTLY AMENDED) A method of treating Alzheimer's disease comprising administering to a host in need of such treatment a therapeutically effective amount of an inhibitor of beta-amyloid production, or a pharmaceutically acceptable salt or pro-drug form thereof, wherein said inhibitor of beta-amyloid production binds to a binding site on a macromolecule involved in the production of beta-amyloid peptide and effects a decrease in production of beta-amyloid peptide;

wherein said binding site is a specific binding site for a compound of Formula (I) of Claim 6 (I-7T) or (I-43T) wherein ~~m is about 2~~ wherein ring B is:



or



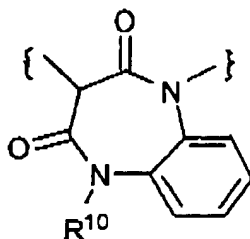
55. (CURRENTLY AMENDED) The method of Claim 54 wherein the macromolecule comprises alpha-, beta-, or gamma-secretase ~~presenilin-1, a fragment of presenilin-1, presenilin-2,~~ or a fragment thereof ~~presenilin-2~~.

56. (CURRENTLY AMENDED) A method of Claim 54 wherein the binding site is a specific binding site for a compound of Formula (I) (I-43T) wherein ~~m is about 2~~ ring B is:

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57. (CURRENTLY AMENDED) The method of Claim 56 wherein the macromolecule comprises alpha -, beta-, or gamma-secretase ~~presenilin-1~~ or a fragment thereof ~~presenilin-1~~.

58. (CURRENTLY AMENDED) The method of Claim 56 wherein the macromolecule comprises gamma-secretase, ~~presenilin-2~~ or a fragment thereof ~~presenilin-2~~.

59. (CURRENTLY AMENDED) A method of in vivo diagnostic imaging comprising administering to a subject a diagnostically effective amount of a radiolabeled inhibitor of Claim 6 of beta-amyloid production.

60. (ORIGINAL) A method of Claim 59 wherein said method is used in the diagnosis of a neurological disease which involves APP processing or elevated levels of beta-amyloid, or both.

61. (ORIGINAL) A method of Claim 59 wherein said method is used in the diagnosis of Alzheimer's disease.

62. (ORIGINAL) A method of Claim 59 wherein the radiolabeled inhibitor is suitable for imaging of the brain of the subject.

63. (ORIGINAL) A method of Claim 59 wherein the radiolabeled inhibitor is radiolabeled with one or more radioisotope selected from ^3H , ^{11}C , ^{14}C , ^{18}F , ^{32}P , ^{35}S , ^{123}I , ^{125}I , or ^{131}I .

64. (ORIGINAL) A method of Claim 59 wherein the inhibitor of beta-amyloid production is a compound selected from any compound disclosed in or within the scope of compounds disclosed in a reference selected from:

- (1) United States patent US 5,703,129;
- (2) PCT application WO98/22441 (or its priority USSN 08/755,444);

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- (3) PCT application WO98/22433 (or its priority USSN 08/807,538);
 - (4) PCT application WO98/22430 (or its priority USSN 08/754,895);
 - (5) PCT application WO98/22493 (or its priority USSN 08/755,334);
 - (6) PCT application WO98/22494 (or its priorities USSN 08/808,528, 08/807,528 or 08/807,427);
 - (7) PCT application WO98/28268 (or its priority USSN 08/780,025);
 - (8) PCT application WO98/38177;
 - (9) PCT application WO95/09838
 - (10) PCT application WO99/67221;
 - (11) PCT application WO99/67220;
 - (12) PCT application WO99/67219;
 - (13) PCT application WO95/66934;
 - (14) PCT application WO00/24392; or
 - (15) Ghosh et al., JACS (2000) 122:3522-2523;
- or any compound which inhibits beta-amyloid production and binds competitively with any of the foregoing compounds in any of the assays described in the Utility section hereof;
- all of which foregoing references are hereby incorporated by reference in their entirety.

65. (CURRENTLY AMENDED) A method of Claim 59 wherein the inhibitor of beta-amyloid production exhibits activity as an inhibitor of gamma-secretase ~~in the method of any of Claim 1.~~

66. - 69. (CANCELLED)

70. (CURRENTLY AMENDED) A method of Claim 59 wherein the inhibitor of beta-amyloid production is selected from:

- ~~(1) an inhibitor of presenilin-1;~~
- ~~(2) an inhibitor of presenilin-2;~~
- (1)~~(3)~~ an inhibitor of β secretase;

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(2) (4) an inhibitor of α secretase; or

(3) (5) an inhibitor of γ secretase; ~~or~~

(6) ~~an inhibitor of BACE/memapsin 2.~~

71. (CURRENTLY AMENDED) A pharmaceutical composition comprising a compound of Claim 6 suitable for in vivo diagnostic imaging comprising a radiolabeled inhibitor of beta-amyloid production.

72. (ORIGINAL) A pharmaceutical composition of Claim 71 wherein the composition is used in the diagnosis of a neurological disease which involves APP processing or elevated levels of beta-amyloid, or both.

73. (ORIGINAL) A pharmaceutical composition of Claim 71 wherein the composition is used in the diagnosis of Alzheimer's disease.

74. (ORIGINAL) A pharmaceutical composition of Claim 71 wherein the radiolabeled inhibitor is suitable for imaging of the brain of the subject.

75. (ORIGINAL) A pharmaceutical composition of Claim 71 wherein the radiolabeled inhibitor is radiolabeled with one or more radioisotope selected from ^3H , ^{11}C , ^{14}C , ^{18}F , ^{32}P , ^{35}S , ^{123}I , ^{125}I , or ^{131}I .

76. (ORIGINAL) A pharmaceutical composition of Claim 71 wherein the inhibitor of beta-amyloid production is a compound selected from any compound disclosed in or within the scope of compounds disclosed in a reference selected from:

- (1) United States patent US 5,703,129;
- (2) PCT application WO98/22441 (or its priority USSN 08/755,444);
- (3) PCT application WO98/22433 (or its priority USSN 08/807,538);
- (4) PCT application WO98/22430 (or its priority USSN 08/754,895);
- (5) PCT application WO98/22493 (or its priority USSN 08/755,334);
- (6) PCT application WO98/22494 (or its priorities USSN 08/808,528, 08/807,528 or 08/807,427);

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(7) PCT application WO98/28268 (or its priority USSN 08/780,025);

(8) PCT application WO98/38177;

(9) PCT application WO95/09838;

(10) PCT application WO99/67221;

(11) PCT application WO99/67220;

(12) PCT application WO99/67219;

(13) PCT application WO95/66934;

(14) PCT application WO00/24392; or

(15) Ghosh et al., JACS (2000) 122:3522-2523;

or any compound which inhibits beta-amyloid production and binds competitively with any of the foregoing compounds in any of the assays described in the Utility section hereof; all of which foregoing references are hereby incorporated by reference in their entirety.

77. [175]. (CURRENTLY AMENDED) A pharmaceutical composition of Claim 71 wherein the inhibitor of beta-amyloid production is ~~selected from:~~

(1) ~~an inhibitor of presenilin-1;~~

(2) ~~an inhibitor of presenilin-2;~~

(3) ~~an inhibitor of β -secretase;~~

(4) ~~an inhibitor of α -secretase;~~

(5) ~~an inhibitor of γ secretase; or~~

(6) ~~an inhibitor of BACE/memapsin-2.~~